

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT**NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 February 1999 (05.02.99)	
International application No. PCT/EP98/03510	Applicant's or agent's file reference 1372PTWO
International filing date (day/month/year) 10 June 1998 (10.06.98)	Priority date (day/month/year) 11 June 1997 (11.06.97)
Applicant ABATANGELO, Giovanni et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
05 January 1999 (05.01.99)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Dominique DELMAS Telephone No.: (41-22) 338.83.38
--	---

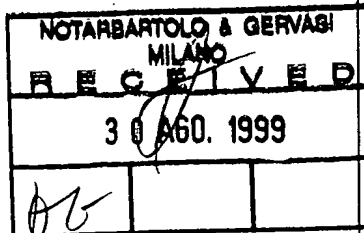
PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

GERVASI, Gemma
Notarbartolo & Gervasi
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) **25. 08. 99**

Applicant's or agent's file reference
1372PTWO

IMPORTANT NOTIFICATION

International application No.
PCT/EP98/03510

International filing date (day/month/year)
10/06/1998

Priority date (day/month/year)
11/06/1997

Applicant
FIDIA ADVANCED BIOPOLYMERS S.R.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0 Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

Oberhauser, A

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1372PTWO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP98/03510	International filing date (day/month/year) 10/06/1998	Priority date (day/month/year) 11/06/1997
International Patent Classification (IPC) or national classification and IPC C12N5/06		
Applicant FIDIA ADVANCED BIOPOLYMERS S.R.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 05/01/1999	Date of completion of this report 25. 08. 99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Deck, A Telephone No. (+49-89) 2399 8432 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/03510

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-15 as originally filed

Claims, No.:

1,2,19-24	as received on	28/05/1999	with letter of	25/05/1999
3-18	as received on	09/08/1999	with letter of	30/07/1999

Drawings, sheets:

1/7-7/7 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/03510

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-24
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Concerning section V:

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: WO 96 33750 A (FIDIA ADVANCED BIOPOLYMERS S.R.L.) 31 October 1996 cited in the application
D2: WO 96 37519 A (FIDIA ADVANCED BIOPOLYMERS S.R.L.) 28 November 1996

1. Novelty, inventive step:

The present application meets the requirements of Article 33 (2) and (3) PCT because a biological material comprising cells and a hyaluronic acid derivative as claimed in claim 1 has neither been described, nor suggested in the available prior art:

- the document D2 describes the use of crosslinked esters of hyaluronic acid for the growth of cells, wherein the carboxy groups of the hyaluronic acid are esterified with aliphatic or araliphatic **mono**alcohols, whereas the present application discloses the use of crosslinked hyaluronic acid esterified with **poly**alcohols (derivatives of claimed group C). The other groups of compounds of the invention are not described in the prior art for the growth of cells.

Therefore, claims 1 to 24 seem to be novel.

- Concerning the inventive step, D2 suggests the use of the claimed hyaluronic acid derivatives for the growth of cells (page 6, lines 11 to 14) without specifying that all the cells grow as well on such support, and without describing experiments concluding to the growth of cells, even the weak cells. Therefore, the skilled person would not use the hyaluronic acid derivatives described in D2 for the growth of weak cells which are particularly difficult to grow (endothelial cells, glandular cells, skin adnexa, germinative cells of hair bulbs). The new biological material of the invention therefore would not have been obvious for the skilled person.

The document D1 describes a different system using one two-dimensional membrane comprising hyaluronic acid derivative for the growth of keratinocytes together with one

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/03510

three-dimensional matrix for the growth of fibroblasts. This system is different from the claimed biological material comprising only one matrix of hyaluronic acid derivative, and does not seem to be appropriate for the growth of weak cells. Therefore, claims 1 to 24 seem to be inventive.

2. Industrial applicability:

For the assessment of the present claims 12 to 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLAIMS**1. A biological material comprising:**

- a) at least one cell type selected from the group consisting of endothelial cells, glandular cells, skin adnexa, germinative cells of hair bulbs; and
- 5 b) a biocompatible and biodegradable three-dimensional matrix comprising at least one hyaluronic acid derivative selected from the group consisting of:
 - A) an ester of hyaluronic acid wherein part or all the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series;
 - 10 B) an autocrosslinked ester of hyaluronic acid wherein a part or all of the carboxy groups are esterified with the alcoholic functions of the same polysaccharide chain or other chains;
 - C) a crosslinked ester of hyaluronic acid wherein a part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating crosslinking by means of spacer chains,
 - 15 D) a hemiester of succinic acid or a heavy metal salt of the hemiester of succinic acid with hyaluronic acid or with partial or total hyaluronic acid esters.
 - 20 E) a sulphated or N-sulphated hyaluronic acid or derivatives thereof.

2. A biological material comprising:

- a) at least one cell type selected from the group consisting of endothelial cells, glandular cells, skin adnexa, germinative cells of hair bulbs, cultivated in presence of a medium treated with fibroblasts or in a co-culture with fibroblasts; and
- 25 b) a biocompatible and biodegradable three-dimensional matrix comprising at least one hyaluronic acid derivative selected from the group consisting of:
 - A) an ester of hyaluronic acid wherein part or all the carboxy functions are esterified with alcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series;
 - 30 B) an autocrosslinked ester of hyaluronic acid wherein a part or all of the carboxy groups are esterified with the alcoholic functions of the same

polysaccharide chain or other chains;

C) crosslinked ester of hyaluronic acid wherein a part or all of the carboxy groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating crosslinking by means of spacer chains;

D) a hemiester of succinic acid or a heavy metal salt of the hemiester of succinic acid with hyaluronic acid or with partial or total hyaluronic acid esters;

E) a sulphated or N-sulphated hyaluronic acid or derivatives thereof.

- 10 3. The biological material according to claim 1 or 2, further containing keratinocytes, collagen and/or fibrin.
4. The biological material according to claim 1 or 2, wherein the endothelial cells are taken from the umbilical vein or from dermis or other tissue wherein blood vessels are present.
- 15 5. The biological material according to claim 1 or 2, wherein the glandular cells are liver cells or Langerhans islet cells.
6. The biological material according to claim 1 or 2, wherein the skin adnexa are sebaceous glands, sweat glands, hair bulbs and the germinative cells are taken from autologous, homologous or heterologous hair bulbs.
- 20 7. The biological material according to claims 1 or 2, wherein the hyaluronic acid ester is a benzyl ester with a degree of esterification of between 25% and 100%.
8. The biological material according to anyone of claims 1-7, wherein component b) is used in the form of a nonwoven fabric, sponges, granules, microspheres, membranes, films, guide channels, gauzes and combinations of the same with one another.
- 25 9. The biological material according to claim 8, wherein component b) is used in the form of a nonwoven fabric.
10. A process for the preparation of a biological material according to claims 1-9, comprising the following steps:
 - 30 i) isolating cells selected from the group consisting of endothelial cells, glandular cells, skin adnexa, germinative cells of hair bulbs and optionally in

the contemporaneous presence of keratinocytes;

ii) preparing a biocompatible and biodegradable three-dimensional matrix comprising at least one hyaluronic acid derivative and optionally collagen and/or fibrin;

5 iii) seeding at least one type of said cells on said matrix optionally in presence of a medium treated with fibroblasts or in a co-culture with fibroblasts.

11. A process for the preparation of a biological material according to claims 2-9, comprising the following steps:

i) isolating endothelial cells from human umbilical vein by enzymatic digestion
10 with collagenase;

ii) amplification on collagen-treated dishes;

iii) preparing a biocompatible and biodegradable three-dimensional matrix comprising at least one hyaluronic acid derivative and optionally collagen and/or fibrin;

15 iv) seeding said endothelial cells, optionally in association with the cells defined in claim 1 or 2, on said matrix optionally in presence of a medium treated with human fibroblasts in primary culture or in a co-culture with human fibroblasts.

12. The biological material according to anyone of claims 1-9, for use in human and veterinary surgery.

20 13. The biological material according to anyone of claims 1-9 wherein component a) comprises endothelial cells alone or in association with skin adnexa, germinative cells or keratinocytes, in skin transplants.

14. The biological material according to claims 1-9, for use in skin and scalp transplants.

25 15. The biological material according to claims 1-9, for use in skin transplants wherein component a) comprising endothelial cells facilitates the mechanism of neo-vascularization of the transplanted skin.

16. The biological material according to anyone of claims 1-9, wherein component a) comprises germinative cells of hair bulbs, for use in scalp transplants.

30 17. The biological material according to anyone of claims 1-9, wherein component a) comprises liver cells, for use in liver tissue transplants.

18. The biological material according to anyone of claims 1-9, wherein component

a) comprises islets of Langerhans, for use in cases of insufficient insulin production.

19. The biological material according to anyone of claims 1-9, wherein component a) comprises endothelial cells, for use in surgery.

5 20. The biological material according to claim 19, for use in cardiovascular, aesthetic and oncological surgery.

21. The biological material according to anyone of claims 19-20, for use in surgery to enhance the biological process of tissue vascularization.

10 22. The biological material according to claims 1-9, for the screening of medicaments or toxic substances.

23. The biological material according to claims 1-9, as a support for gene transfection.

24. The biological material according to claim 23, for use in gene transfection.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1372PTWO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 98/ 03510	International filing date (day/month/year) 10/06/1998	(Earliest) Priority Date (day/month/year) 11/06/1997
Applicant FIDIA ADVANCED BIOPOLYMERS S.R.L. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
- ☐ filed with the international application.
☐ furnished by the applicant separately from the international application.
☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
- ☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

HYALURONIC ACID DERIVATIVE BASED CELL CULTURE MATRIX AND BIODEGRADABLE THREE-DIMENSIONAL MATRIX

5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.
☐ because the applicant failed to suggest a figure.
☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03510

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N5/06 C12N5/08 A61L27/00 G01N33/50 A61K48/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N A61L G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 33750 A (FIDIA ADVANCED BIOPOLYMERS S.R.L.) 31 October 1996 cited in the application see page 9, line 25 - page 10, line 22; claims 1-10,14-18; example 1 ---	1,2, 6-14,16, 18,26-28
A	WO 96 37519 A (FIDIA ADVANCED BIOPOLYMERS S.R.L.) 28 November 1996 see claims 1-5,12-17 ---	1-28
A	EP 0 529 659 A (SEIKAGAKU KOGYO K.K.) 3 March 1993 see claims --- -/--	1-28

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

22 October 1998

Date of mailing of the international search report

29/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ryckebosch, A

INTERNATIONAL SEARCH REPORT

Intern. al Application No

PCT/EP 98/03510

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>R. CORTIVO ET AL.: "IN VITRO STUDIES ON BIOCOMPATIBILITY OF HYALURONIC ACID ESTERS." BIOMATERIALS. vol. 12, October 1991, pages 727-730, XP002027830 GUILDFORD GB see the whole document -----</p>	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internationall Application No

PCT/EP 98/03510

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633750 A	31-10-1996	IT PD950083 A AU 5647996 A CA 2219272 A EP 0822839 A	28-10-1996 18-11-1996 31-10-1996 11-02-1998
WO 9637519 A	28-11-1996	IT PD950101 A AU 6001296 A	22-11-1996 11-12-1996
EP 529659 A	03-03-1993	JP 5236951 A AU 654376 B AU 2138592 A CA 2077175 A FI 923874 A US 5624839 A	17-09-1993 03-11-1994 11-03-1993 01-03-1993 01-03-1993 29-04-1997

PATENT COOPERATION TREATY

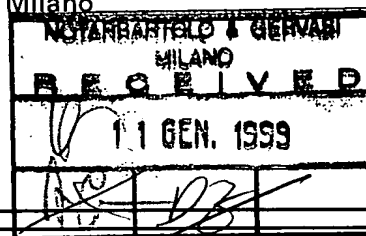
PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

PASSINI, Angelo
Notarbartolo & Gervasi
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

Date of mailing (day/month/year) 17 December 1998 (17.12.98)		
Applicant's or agent's file reference 1372PTWO		
International application No. PCT/EP98/03510	International filing date (day/month/year) 10 June 1998 (10.06.98)	Priority date (day/month/year) 11 June 1997 (11.06.97)
Applicant FIDIA ADVANCED BIOPOLYMERS S.R.L. et al		

IMPORTANT NOTICE

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU, BR, CA, CN, EP, IL, JP, KP, KR, PL, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AL, AM, AP, AT, AZ, BA, BB, BG, BY, CH, CU, CZ, DE, DK, EA, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, OA, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 17 December 1998 (17.12.98) under No. WO 98/56897

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year) 17 December 1998 (17.12.98)	IMPORTANT NOTICE
Applicant's or agent's file reference 1372PTWO	International application No. PCT/EP98/03510
<p>The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.</p>	

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

PASSINI, Angelo

Notarbartolo & Gervasio

Corso di Porta Vittoria, 9

I-20122 Milano

ITALIE

RECEIVED	
15 FEB. 1999	
<i>[Signature]</i>	<i>[Signature]</i>

Date of mailing (day/month/year)

05 February 1999 (05.02.99)

Applicant's or agent's file reference

1372PTWO *P. f. Arch*

IMPORTANT INFORMATION

International application No.

PCT/EP98/03510

International filing date (day/month/year)

10 June 1998 (10.06.98)

Priority date (day/month/year)

11 June 1997 (11.06.97)

Applicant

FIDIA ADVANCED BIOPOLYMERS S.R.L. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP : GH, GM, KE, LS, MW, SD, SZ, UG, ZW

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

National : AU, BG, BR, CA, CN, CZ, DE, GB, IL, JP, KP, KR, MN, NO, NZ, PL, RO, RU, SE, SK, US,
VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

National : AL, AM, AT, AZ, BA, BB, BY, CH, CU, DK, EE, ES, FI, GE, GH, GM, GW, HU, ID, IS, KE,
KG, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MW, MX, PT, SD, SG, SI, SL, TJ, TM, TR, TT, UA,
UG, UZ, YU, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Dominique DELMAS *[Signature]*

Telephone No. (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

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International Application No. **PCT/EP 98 / 03510**

International Filing Date **(10.06.98) 10 JUN 1998**

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PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) **1372PTWO**

Box No. I TITLE OF INVENTION BIOLOGICAL MATERIAL COMPRISING AN EFFICACIOUS CELL CULTURE AND A BIOCOMPATIBLE AND BIODEGRADABLE THREE-DIMENSIONAL MATRIX CONSISTING OF A HYALURONIC ACID DERIVATIVE

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)

FIDIA ADVANCED BIOPOLYMERS S.r.l.
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☐ This person is also inventor.

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Facsimile No.

Teleprinter No.

State (i.e. country) of nationality:
IT

State (i.e. country) of residence:
IT

This person is applicant for the purposes of:

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☒ all designated States except the United States of America

☐ the United States of America only

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Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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This person is:

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☐ inventor only (If this check-box is marked, do not fill in below.)

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The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

PASSINI Angelo
NOTARBARTOLO & GERVASI
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Telephone No.

Facsimile No.

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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This person is:

☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (i.e. country) of nationality:
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State (i.e. country) of residence:
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This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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This person is:

☐ applicant only
☐ applicant and inventor
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Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box <input type="checkbox"/>	
The priority of the following earlier application(s) is hereby claimed:			
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item (1) ITALY	(11.06.97) 11th June 1997	PD 97 A 000122	
item (2)			
item (3)			
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required): <input type="checkbox"/> The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / _____ Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request: Country (or regional Office): _____ Date (day/month/year): _____ Number: _____			
Box No. VIII CHECK LIST			
This international application contains the following number of sheets: 1. request : 4 sheets 2. description : 15 sheets 3. claims : 4 sheets 4. abstract : 1 sheets 5. drawings : 7 sheets <hr/> Total : 31 sheets		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> separate signed power of attorney 2. <input type="checkbox"/> copy of general power of attorney 3. <input type="checkbox"/> statement explaining lack of signature 4. <input checked="" type="checkbox"/> priority document(s) identified in Box No. VI as item(s): _____ 5. <input type="checkbox"/> fee calculation sheet 6. <input type="checkbox"/> separate indications concerning deposited microorganisms 7. <input type="checkbox"/> nucleotide and/or amino acid sequence listing (diskette) 8. <input checked="" type="checkbox"/> other (specify): _____ accompanying letter	
Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).			
Milan, Italy, June 9, 1998		PASSINI Angelo <i>Passini Angelo</i>	

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C12N 5/06, 5/08, A61L 27/00, G01N 33/50, A61K 48/00	A1	(11) International Publication Number: WO 98/56897 (43) International Publication Date: 17 December 1998 (17.12.98)
(21) International Application Number: PCT/EP98/03510 (22) International Filing Date: 10 June 1998 (10.06.98) (30) Priority Data: PD97A000122 11 June 1997 (11.06.97) IT (71) Applicant (for all designated States except US): FIDIA ADVANCED BIOPOLYMERS S.R.L. [IT/IT]; Via De' Carpenteri, 3, I-72100 Brindisi (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): ABATANGELO, Giovanni [IT/IT]; Via Pelosa, 32, I-35050 Saccolongo (IT). CALLEGARO, Lanfranco [IT/IT]; Via Monte Grappa, 6, I-36016 Thiene (IT). (74) Agent: PASSINI, Angelo; Notarbartolo & Gervasi, Corso di Porta Vittoria, 9, I-20122 Milano (IT).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: HYALURONIC ACID DERIVATIVE BASED CELL CULTURE AND BIODEGRADABLE THREE-DIMENSIONAL MATRIX		
(57) Abstract <p>The present invention relates to a biological material comprising a matrix consisting of at least one derivative of hyaluronic acid on which endothelial cells, glandular cells such as islets of Langerhans and liver cells, skin adnexa, germinative cells of hair bulbs, and keratinocytes are grown, optionally in presence of a medium treated with fibroblasts or in a co-culture with fibroblasts. It is also described the process for the production of said biological material and its use for human and veterinary use, in cardiovascular and oncological surgery, in transplants, to enhance the biological process of tissue vascularization and for aesthetic use, and also for the screening of medicaments or toxic substances and as a support gene transfection. Biological material comprising an efficacious cell culture and a biocompatible and biodegradable three-dimensional matrix consisting of a hyaluronic acid derivative.</p>		

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